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Compounds for the modulation of the glycolysis enzyme and/or transaminase complex

Background of the invention.

The invention relates to compounds for the modulation of the glycolysis enzyme and/or transaminase complex and thus in particular to the growth inhibition of cells and/or bacteria, pharmaceutical compositions containing such compounds as well as uses of such compounds for preparing pharmaceutical compositions for treating various diseases.

Background of the invention.

Cancer today is one of the most frequent causes of death, and the number of cancer cases in the industrialized countries continuously grows. This is mainly based on the fact that malignant tumors are a disease of higher age, and due to a successful controlling of infection diseases, more people will reach this age. In spite of all progress in the diagnostic and therapeutic field, the healing chances for most frequent inner cancer types are seldom higher

than 20%. A cancerous tumor nowadays can be destroyed or inhibited in its growth. A re-conversion of a tumor cell into a normal cell is however not yet possible. The most important therapeutic measures, the operation and the irradiation, remove cancer cells from the organism. The presently used chemotherapeutic agents of the cancer, the cytostatics, also lead to a destruction or damaging of tumor cells only. In most cases the effect is so little specific that simultaneously heavy damages to healthy cells will occur.

In general, tumor cells have a metabolism differing from healthy cells, in particular glycolysis. Thus, a change of the isoenzyme system involved in the glycolysis and a change of the transport of NADH is typical for tumor cells. Among other effects, the activity of the enzymes of the glycolysis is increased. This permits high reaction rates under the aerobic conditions typical for tumor cells. For details, reference is made to E. Eigenbrodt et al., Biochemical and Molecular Aspects of Selected Cancers, Vo. 2, p. 311 ff, 1994.

Different other diseases mentioned below are either characterized by an (excessive) metabolism by the glycolysis enzyme complex or can be treated by the reduction or inhibition thereof.

Prior art.

From the document E. Eigenbrodt et al., Biochemical and Molecular Aspects of Selected Cancers, Vo. 2, p. 311 ff, 1994 it is known that

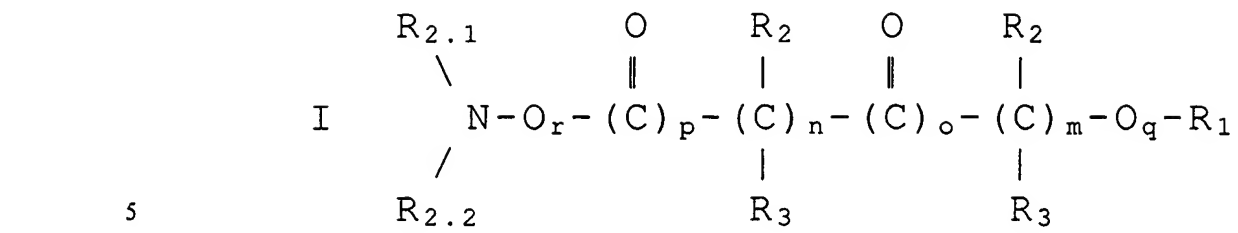
glucose analogs are used for inhibiting the glycolysis. Other approaches known herefrom are the use of inhibitors of glycolytical isoenzymes, for instance by suitable chelation or inhibition of chelations. As a result, the tumor cells are so to speak starved out. It is a problem with the above compounds that many of them are genotoxic and/or not sufficiently specific for tumor cells.

Technical object of the invention.

It is the technical object of the present invention to specify active ingredients being able to modulate or inhibit the glycolysis enzyme and transaminase complex, in particular the proliferation of cancer cells and to thus inhibit the growth of neoplastic tumors as well as defense over-reactions of the body, such as septic shock, autoimmune diseases, transplant rejections as well as acute and chronic inflammatory diseases, and that simultaneously with only slight to no cytotoxicity at all with regard to cells having an intact glycolysis enzyme complex or other complex structures. In addition, it is intended to inhibit the growth of unicellular organisms.

Basics of the invention.

For achieving said technical object, the invention teaches a compound according to formula I



wherein R1 = -CN, -COO+, -COS+, -COOH, -COSH, -COOR1.1, -COSR1.1, wherein R1.1 = -H, C1-10 alkyl, C1-10 aralkyl or aryl, wherein R2 = -H, -OR1.1, -Hal (-F, -Cl, -Br, -J), NR2.1R2.2, -Am, -O-Am, -S-Am, wherein R3 = -H, -OR1.1, -Hal (-F -Cl, -Br, -J), NR2.1R2.2, -Am, -O-Am, -S-Am, wherein R2.1 = -H, C1-10 alkyl, C1-10 aralkyl or aryl, wherein R2.2 = -H, C1-10 alkyl, C1-10 aralkyl or aryl, wherein R2.1 and R2.2 may be identical or different, wherein n and m may be identical or different and 0 to 10, wherein o and p may be identical or different and 0 to 3, wherein o > 0, if n and m = 0, wherein R2 and R3 may be identical or different for Cn and Cm, wherein R2 may be identical or different for every Cx = 1 ... n, wherein R3 may be identical or different for every Cy = 1 ... m, wherein -Am is an amino acid radical, wherein q and r = 0 or 1 and identical or different, wherein $-O_r-$ and/or $-O_q-$ may also be replaced by $-S_r-$ or $-S_q-$, resp., wherein -NR2.1R2.2 may be replaced by a linear or branched -C1-C20 alkyl, or a physiologically well tolerated salt of such a compound.

An amino acid radical is defined in an amino acid as follows: NH_2-CHAm-COOH. These are in particular amino acid radicals of the proteinogenic amino acids, especially of the essential amino acids. As far as a compound according to the invention has an optical activity (for instance according to embodiments of claim 3), the

various variants such as L and D types are also included. Corresponding considerations apply in the case of (several) chiral centers.

Particularly suited are compounds according to the invention, wherein R2 exists at least singly as -Am, wherein -Am preferably represents an amino acid radical of an essential amino acid, wherein in particular q = 0 and r = 1 or q = 1 and r = 0 or q = 1 and r = 1, m = 1, R3 = -H, n = o = p = 0, R2.1 = R2.2 = -H.

Further, various specific groups are preferred, namely: i) wherein n = o = p = 0, wherein m = 0 to 4, wherein R2 = R3 = -H, wherein R2.1 = R2.2 = -H, wherein q = 0 and r = 1, ii) wherein m = p = 0, wherein o = 1, wherein n = 0 to 4, wherein R2 = H, wherein R3 = -H or -Hal in the case Cx = 1, wherein R3 = -H for all Cx = n > 1, wherein R2.1 = R2.2 = -H, wherein q = 0 and r = 1, iii) wherein m = 1 to 4, wherein n = o = p = 0, wherein R2 = H, wherein R3 = -H or -Hal in the case Cy = 1, wherein R3 = -H for all Cy = m > 1, wherein R2.1 = R2.2 = -H, wherein q = 0 and r = 1, iv) wherein o = p = 1, wherein m = 0, wherein n = 0 to 4, wherein R2 = R3 = -H, wherein R2.1 = R2.2 = -H, wherein q = 0 and r = 1, v) wherein n = p = 0, wherein o = 1, wherein m = 0 to 4, wherein R2 = R3 = -H, wherein R2.1 = R2.2 = -H, wherein q = 0 and r = 1, or vi) wherein m = p = 0, wherein o = 1, wherein n = 1 to 4, wherein R2 = R3 = -H, wherein R2.1 = R2.2 = -H, wherein q = 0 and r = 1.

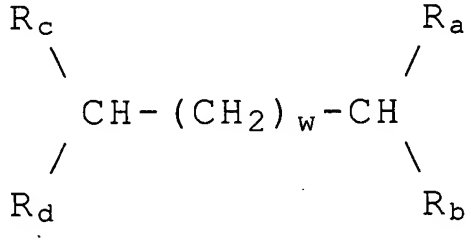
Generally, one R2 may be replaced by -Am.

Examples for compounds wherein -NR2.1R2.2 is replaced by -C1-C20 alkyl are: CH_3-O-$(CH_2)_m$-R1, CH_3-O-CO-$(CH_2)_m$-R1, CR5R6R7-O-$(CH_2)_m$-R1, CR5R6R7-O--CO-$(CH_2)_m$-R1, wherein R5, R6 and R7 may be -C1-C10 alkyl, linear or branched, not substituted or substituted. (CH_2) may of course also be (CR2R3). -O- or =O may be replaced by -S- or =S. R1 is as specified above. CR5R6R7 may in particular be t-butyl.

Examples for the compounds according to the invention are: NH_2-O-$(CH_2)_m$-R1, NH_2-O-$(CH_2)_n$-CO-R1, NH_2-O-CHHal-$(CO)_o$-R1, NH_2-O-CHHal-CH_2-$(CO)_o$-R1, NH_2-O-CHHal-$(CH_2)_2$-$(CO)_o$-R1, NH_2-O-CHHal-$(CH_2)_3$-$(CO)_o$-R1, NH_2-O-CHHal-$(CH_2)_4$-$(CO)_o$-R1, NH_2-O-CO-$(CH_2)_n$-CO-R1, NH_2-O-CO-$(CH_2)_n$-R1, NH_2-O-$(CH_2)_n$-CO-R1, NH_2-O-CO-$(CH_2)_n$-$CHNH_2$-R1, NH_2-O-$(CH_2)_n$-$CHNH_2$-R1, with R1 = -CN or -COOH, m or n = 0 to 4, o = 0 or 1, wherein -O- may be replaced by S.

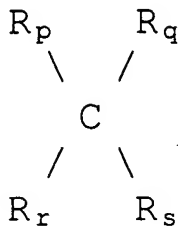
Another formula according to the invention is formula II

II



wherein R_a = -CN, R_b = -H, =O, -OH, $-NH_2$, R_c = -NH_2, -O-NH_2, -O-(C1-10)alkyl, R_d = -H, -Hal, =O, -OH, wherein the case of =O H the one CH is omitted, wherein w = 0 to 10, e.g. 1 to 4.

Another formula according to the invention is formula III

III 

wherein Rp = -R1, -O-R1, -O-$(CR2R3)_x$-R1, -$(CR2R3)_x$-O-R1, R_q = -NR2.1R2.2, -O-NR2.1R2.2, -O-$(CR2R3)_x$-NR2.1R2.2, -$(CR2R3)_x$-O-NR2.1R2.2, R_r = -Am, -O-Am, -O-$(CR2R3)_x$-Am, -$(CR2R3)_x$-O-Am, - R_s = -H, -C1-C10 alkyl, aryl or aralkyl, -C1-C10 hydroxyalkyl, aryl or aralkyl, or an ether of such a hydroxy radical, wherein -O- may be replaced by -S- and x = 1 to 10, in particular 1 to 4. R1 is as specified above, in particular -CN or -COOH. Examples of such compounds are: NH_2-O-CHAm-R1, NH_2-CHAm-O-R1, NH_2-O-CHAm-O-R1, NH_2-CHR1-O-Am, Am-O-$CHNH_2$-O-R1, NH_2-O-(Am-O-CH-O-R1). On one side of one -O- or several -O- or on both sides of one -O- or several -O- immediately -$(CH_2)_x$- may be interposed.

Compounds according to the invention may be present in an ionized condition in a solution, depending on the pH value (e.g. as $-COO^-$ in basic condition or $-NH_3^+$ in acid condition). Salts, such as hydrochlorides, may also be formed.

The invention is based on the finding that beside the classic metabolic diseases, such as diabetes mellitus, adiposity, other diseases, too, such as cancer, autoimmune diseases and

rheumatism are caused by metabolic defects. This explains the strong influence of the food on these diseases. A directly measurable biochemical parameter for these metabolic ketoacidoses is the increase of pyruvate kinase type M2 (M2-PK) growing in the blood of all diseases above and below. In dependence from the respective disease, the M2-PK detectable in the blood of the patients originates from different cells: for cancer from tumor cells, for sepsis from immune cells, for rheumatism from immune and/or synovial cells. In healthy cells, there are tetrameric forms of the M2-PK in a high-order cytosolic complex, the glycolysis enzyme complex. By the over-activation of oncoproteins, there is an emigration of the M2-PK out of the complex and the typical changes in the tumor metabolism. Simultaneously, the phosphoglyceromutase (PGM) leaves the complex and migrates into another enzyme complex, where the cytosolic transaminases are associated (see example 2). This complex is therefore called transaminase complex. The substrate of the PGM, glycerate-3-P, is the first stage for the synthesis of the amino acids serine and glycine. Both amino acids are essential for the DNA and polypholipid synthesis. By the immigration of the PGM into the transaminase complex, the synthesis of serine from glutamate and thus the glutaminolysis is activated. The same changes take place in immune cells, if the immune system fails, such as for instance in the case of rheumatism, sepsis or polytrauma. The integration of the metabolism of different cells in multi-cellular organisms takes place by organ-specific association of the enzymes in the cytosol: in the muscle for instance by association with contraction proteins. For this reason, the different organs are pro-

vided with respectively specific isoenzymes. The dissolution of this order will necessarily lead to diseases. Uni-cellular organisms, such as bacteria or yeasts reacting on a sufficient offer of food with dissipated proliferation, do not have a complex organization of the cytosol. As a consequence, substances inhibiting the failing metabolism of multi-cellular organisms, will also inhibit the proliferation of such unicellular organisms.

The invention further teaches the use of a compound according to the invention for preparing pharmaceutical compositions for treating one or several diseases of the group comprising "cancer, chronic inflammations, asthma, arthritis, osteoarthritis, chronic polyarthritis, rheumatic arthritis, inflammatory bowl disease, degenerative joint diseases, rheumatic diseases with cartilage disorders, sepsis, autoimmune diseases, type I diabetes, Hashimoto thyreoiditis, autoimmune thrombocytopenia, multiple sclerosis, myasthenia gravis, chronically inflammatory intestinal diseases, Crohn's disease, uveitis, psoriasis, collagenoses, Goodpasture syndrome, diseases with disturbed leukocyte adhesion, cachexia, diseases by increased TNF-alpha concentration, diabetes, adiposity, bacterial infections, in particular with resistant bacteria". The term treatment also comprises the prophylaxis.

The invention further teaches a pharmaceutical composition, wherein a compound according to the invention is mixed with one or several physiologically well tolerated auxiliary substances and/or carrier substances and galenically prepared for the local or systemic admini-

stration, in particular oral, parenteral, for the infusion into a target organ, for the injection (e.g. IV, IM, intracapsular or intralumbal), for the application in tooth pockets (space between tooth root and gum).

The invention finally teaches the use of a compound according to the invention for inhibiting in vitro the glycolysis enzyme complex, in particular of pyruvate kinase, asparaginase, serine dehydratases, transaminases, desaminases and/or glutaminases. In particular, the transamination, the oxidative deamination, the hydrolytic deamination, the eliminating deamination, and the reductive deamination are blocked.

It is understood that if applicable, there may exist stereoisomers for the compounds according to formula I, such stereoisomers all being covered by the invention. The term alkyl comprises linear and branched alkyl groups as well as cycloalkyl, if applicable also cycloalkyl groups having linear or branched alkyl substituents. The term aryl also comprises aralkyl groups, and alkyl substituents may be alkyl or cycloalkyl.

Surprisingly it has been found that compounds according to the invention are able to competitively inhibit the above members of the glycolysis enzyme complex. The proliferation of cancer cells in therapeutically relevant concentrations can be inhibited. There are no cytotoxic effects to be expected in the respective dosage range. Because of their pharmacological properties the compounds according to the invention are also excellently suitable for the treatment and prophylaxis of the above further diseases. In con-

junction with the indications for the inhibition of inflammations or antirheumatic effects, it is of a special relevance that the substances according to the invention are non-steroidal substances.

The inhibition of the glycolysis enzyme and of the transaminase complex in particular comprises the inhibition of the metabolic activity and the energy gain from serine, glutamine, ornithine, proline and arginine or from other amino acids of this and other families, but also the synthesis of such amino acids used for energy generation; important energy sources for instance in tumor cells, but also in bacteria and yeasts. The cells or bacteria or yeasts are so to speak starved out. In detail, substances according to the invention block for instance the following reactions: i) threonine to glycine, ii) threonine to α-amino-β-ketobutyrate, iii) α-amino-β-ketobutyrate to glycine, iv) serine pyridoxalphosphate (PLP) Schiff's base to aminoacrylate, in particular folic acid-dependent serine hydroxymethyltransferase, v) aminoacrylate to pyruvate (by displacement of the balance of the natural hydrolysis of the PLP Schiff's base to the Schiff's base), vi) transamination by means of PLP for the synthesis of an amino acid from an oxo acid, in particular of the branch-chained transaminase, the α-ketoglutarate, oxalacetate, 3-hydropyruvate and glyoxalate transaminase, the glutamate dehydrogenase. In particular, the formation of pyruvate from amino acids is inhibited by substances according to the invention. Important is the release of NH_2-OH or CH3-OH (-H to C or N if applicable replaced by other radicals, for instance alkyl) by glutaminase, arginase, asparaginase or serine

hydroxymethyltransferase. This will lead to an increased specificity, since a feature of tumor cells is a high glutaminase and serine hydroxymethyltransferase activity. NH_2-OH (hydroxylamine, HA) for instance can be phosphorylated by the high pyruvate kinase activities instead of the -OH of the phosphate (e.g. of the ADP). This will lead to a decoupling of the pyruvate kinase reaction in tumor cells. Therefore, the invention in all generality also comprises all natural metabolites of the substances according to the invention, in particular of the aminooxyacetate, i.e. fractions of these substances.

In the transaminase complex, in addition to the PGM and NDPK, the cytosolic isoforms of the glutamate oxalacetate transaminase (GOT), glutamate pyruvate transaminase (GPT), glutamate dehydrogenase (GIDH) and malate dehydrogenase (MDH) are associated. GOT and MDH are components of the malate-aspartate shuttle, by which the hydrogen produced in the cytosol is transported into the mitochondria. NAD+ is recycled for the cytosolic glyceraldehyde 3-phosphate dehydrogenase reaction. The malate-aspartate shuttle is part of the glutaminolysis. For an active malate-aspartate shuttle, in addition to GOT, the presence of the p36-bound form of the MDH is important, as represented in example 3.

Various further embodiments of the invention are possible. For instance, a pharmaceutical composition according to the invention may comprise several different compounds of the above definitions. Furthermore, a pharmaceutical composition according to the invention may in addition comprise an active ingredient being differ-

ent from the compound of formula I. Then it is a combination preparation. Therein, the various employed active ingredients may be prepared in a single type of administration, i.e. the active ingredients are mixed in the type of administration. It is however also possible to prepare the various active ingredients in spatially separated types of administration of identical or different species.

As counterions for ionic compounds according to formula I Na^+, K+, Li+, cyclohexylammonium or basic amino acids (e.g. lysine, argini, ornithine, glutamine) can be used.

Drugs prepared by the method according to the invention may be administered in an oral, intramuscular, periarticular, intraarticular, intravenous, intraperitoneal, subcutaneous or rectal manner.

The invention also relates to methods for preparing drugs which are characterized by that at least one compound of formula I is brought into a suitable dosage form by using a pharmaceutically suitable and physiologically well tolerated carrier and if applicable further suitable active ingredients, additional or auxiliary substances.

Suitable solid or liquid dosage forms are for instance granulates, powders, dragées, tablets, (micro) capsules, suppositories, syrups, juices, suspensions, emulsions, drops or injectable solutions as well as preparations with protracted release of the active ingredient, for the preparation of which usual means such as carrier substances, explosion, binding, coating, swelling,

sliding or lubricating agents, flavoring substances, sweeteners and solution mediators are used.

Auxiliary substances are for instance magnesium carbonate, titanium dioxide, lactose, mannite and other sugars, talcum, milk protein, gelatin, starch, cellulose and its derivatives, animal and plant oils such as cod-liver oil, sunflower, peanut or sesame oil, polyethylene glycols and solvents, such as sterile water and one or poly-valent alcohols, e.g. glycerin.

Preferably the drugs are prepared and administered in dosage units, each unit containing as an active component a defined dose of the compound according formula I of the invention. With solid dosage units such as tablets, capsules, dragées or suppositories, this dose may be 1 to 1,000 mg, preferably 50 to 300 mg, and for injection solutions in an ampule form 0.3 to 300 mg, preferably 10 to 100 mg.

For treating an adult patient of 50 to 100 kg weight, for instance 70 kg, for instance daily doses of 20 to 1,000 mg active ingredient, preferably 100 to 500 mg, are indicated. Under certain circumstances, higher or lower daily doses may be recommendable. The administration of the daily dose may be a one-off administration in the form of a single dosage unit or several smaller dosage units as well as a multi-administration of separated doses in certain intervals.

In the following, the invention is explained in more detail with reference to examples representing embodiments only.

Example 1: Quantification of the effectivity of a compound according to the invention.

Suitable Novikoff hepatoma cells are obtainable from the tumor bank of the Deutsches Krebsforschungszentrum, Heidelberg (Cancer Research 1951, 17, 1010). 100,000 cells each are sown out per 25 cm^2 cultivation bottle. A substance according to the invention, dissolved in a solvent suitable for use in cell cultures, for instance water, diluted ethanol, dimethylsulfoxide or the like, is added in an increasing concentration to the culture medium, e.g. in a concentration range of 80 µM - 5,000 µM or of 100 µM - 300 µM. After four days of cultivation, the number of cells per bottle is counted. In comparison to the control sample (without addition of a compound according to the invention or instead with addition of a reference compound), the measure and the dose dependence of a proliferation inhibition of the used compound can be seen.

Example 2: Emigration of the PGM.

In Fig. 1a is shown an isoelectric focusing of a tumor cell extract (MCF-7 cells). It can be seen that PGM leaves the glycolysis enzyme complex and migrates into a complex associated with the cytosolic transaminases, the transaminase complex. The transaminase complex is built up as follows: cytosolic glutamate oxalacetate transaminase (GOT), c-malate dehydrogenase (MDH),

phosphoglyceromutase (PGM). Not shown are: c-glutamate pyruvate transaminase (GPT), c-glutamate hydroxypyruvate transaminase, c-alanine hydroxypyruvate transaminase, c-serine hydroxymethyl transferase and c-glutamate dehydrogenase (GIDH). The PGM and the nucleotide diphosphate kinase (NDPK) may be associated in the transaminase as well as in the glycolysis enzyme complex.

Example 3: Inhibition of the malate-aspartate shuttle.

In Fig. 1b is shown the effect of aminoacetate (AOA) and hydroxylamine (HA) on the activity of the cytosolic and mitochondrial isoenzyme of the GOT in vitro. The isoenzymes of the GOT were dissociated by an isoelectric focusing. It can be seen that aminooxyacetate mainly inhibits the cytosolic isoenzyme, and hydroxylamine inhibits both isoenzymes of the GOT. The inhibition of the GOT leads to an inhibition of the malate-aspartate shuttle. As a consequence, NAD cannot be recycled, and the glycolysis is inhibited at the stage of the GAPDH.

The following explanations are independent from the above examples. The invention further teaches the use of N-(4'-trifluoromethylphenyl)-5-methylisoxazole-4-carboxamide ($C_{12}H_9F_3N_2O_2$; MW 270.2, see also Fig. 2a) and/or its natural active metabolites A 77 1726 according to Fig. 2b for preparing a pharmaceutical composition for treating tumor diseases, in particular solid

tumors. The benzene ring may, alternatively to the shown substitution with -CF3, generally be singly, doubly, triply, quadruply or quintuply substituted with -Chal3 or -O-Chal3 or -Hal at an arbitrary position. The pharmaceutical composition according to the invention is particularly suited for treating large tumors, i.e. beginning from 0.1 to 1 cm^3 tumor size. A pharmaceutical composition according to the invention is for instance prepared for oral administration, for instance with the following auxiliary and carrier substances: colloidal SiO_2, crospovidone, hydroxypropylmethyl cellulose, lactose monohydrate, magnesium stearate, polyethylene glycol, povidone, starch, talcum, TiO_2 and/or yellow iron oxide. The dosage is 1 to 50 mg per day, preferably 10 to 30 mg. It may be recommended to administer in a therapy initially a starting dose of 20 to 500 mg, in particular 50 to 150 mg, for the first 1 to 10 days, in particular the first 1 to 3 days. In another embodiment of the invention, the substance mentioned above is combined with one or several sugar phosphates, for instance fructose-1,6-biphosphate, glycerate-2,3-biphosphate, glycerate-3-phosphate, ribose-1,5-biphosphate, ribulose-1,5-biphosphate, and the combination of substances in a dosage form, for instance a tablet, may be mixed. It is however also possible to provide the components separately in identical or different dosage forms. The sugar phosphate may be administered in a dosage of 20 to 5,000 mg per day, for instance 100 to 500 mg.

These variants of the invention surprisingly lead to an inhibition of the growth of tumor cells and tumor tissue, since these substances

or the metabolite can bind to the pyruvate kinase and inhibit or reverse the energy metabolism failing for tumor cells. From this situation there results a special advantage in that these substances specifically influence the metabolism of tumor cells and not or to a lower degree that of normal cells, and that there are thus only slight side effects if at all.

The effectivity of these substances is surprising because the known effect as a pyrimidine synthesis inhibitor relates to a completely different effective mechanism, and the phenomenological observation of an anti-proliferative effect is substantially directed toward immune cells and cells related to inflammatory diseases.

Of a special importance is a combination of one or several of the active ingredients mentioned on the previous page with one or several of the active ingredients mentioned further above or aminooxyacetate (AOA, NH2-O-CH2-COOH, salts or esters thereof, for instance C1-C10 alkyl or hydoxyalkyl esters). For instance AOA is particularly effective for small tumors (< 0.1 to 1 cm^3) or prevents the development thereof, in particular development of metastases, whereas compounds of the formulas 10 or 11, if applicable in combination with sugar phosphate, is effective for the large tumors. The reason for this are the different metabolisms in small and large tumors. The above explanations for combinations apply in an analogous manner.

Substances according to the invention can further be used for preparing a pharmaceutical composition for treating heart insufficiency or

the chronic cardiac failure (CCF). These are the variants defined by the New York Heart Association (NYHA) Classification or grades from NYHA I to NYHA IV. All these diseases are acute and/or chronic failure of the heart muscle to provide under load or even already at rest for the blood circulation or the transportation capacity required for the metabolism of the organism. The reasons are the insufficient glycolysis by glucose deficiency in the heart muscle and/or its insufficient oxygen supply and complex coronary inflammation processes (activation of cells of the immune system and complement). This aspect of the invention is based on the finding that by the substances according to the invention alternative energy-generating biochemical processes are modulated, and that is thus also possible to produce so to speak replacement pathways for the above insufficiently operating processes, for instance by activation of the serinolysis and glutaminolysis or to displace by substances according to the invention the existing dynamic balance between glycolysis on the one hand and glutaminolysis on the other hand in favor of the glycolysis, under simultaneous administration of oxygen (increase of the oxygen partial pressure in the blood, for instance by breathing). In this context, the administration of anti-inflammatory substances according to the invention can prevent the imminent highly dangerous acidosis (by lactate production). Compared to prior art measures, such as administration of ACE inhibitors, diuretics, digitalis, positive inotropic substances or isosorbide dinitrate, the substances according to the invention directly influence the energy metabolism, and the latter is improved. Side effects are as a consequence comparatively weak.

In this context, it has been found by the invention that at least in the cases of the NYHA grade II to IV the concentration of tumor M2-PK (= M2-PK dimeric in contrast to standard M2-PK being tetrameric) in cells and/or the blood increases, which as a routine process can easily be determined, other than by the methods usual up to now. Therefore the invention further teaches the use of a tumor M2-PK detecting test system for preparing a diagnostic substance for the in vitro diagnosis of a heart insufficiency, in particular also of the grade or the inflammatory processes connected therewith. If for a patient increased M2-PK values (sick collective) are found in the blood plasma compared to standard values (defined maximum limits; normal collective), this is indicative for the existence of a heart insufficiency and/or for inflammatory processes correlated therewith, at least however for the risk to suffer from a heart insufficiency. Such a blood plasma analysis can easily and quickly be performed. Compared thereto, previous standard methods (gold standard, blood gas analysis) are not suitable for routine tests and are expensive. For this aspect of the invention, any known test systems can be used which detect tumor M2-PK, e.g. immunological test systems with antibodies. In particular, per se known test systems can be used which detect tumor M2-PK as a tumor metabolism marker, for instance monoclonal antibodies being specific herefor.

Various substances which can be used according to the invention are shown in the further figures. In particular the essential variation possibilities are represented in an exemplary manner, the permutations easily deductible therefrom not being shown for the sake of

simplicity. The invention finally also comprises all natural metabolites of the described substances.

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